# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2004/017736 | 04.06.2004 | 05.06.2003 |

International Patent Classification (IPC) or both national classification and IPC
C07K14/32, A61K39/07, A61P31/04, C07K16/12

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Form PCT/ISA/237 (Cover Sheet) (January 2004)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/017736



**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/017736

**Box No. II Priority**

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-27 (with respect to Industrial Applicability)

because:

☒ the said international application, or the said claims Nos. 20-27 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 6,10 |
| | No: | Claims | 1-5,7-9,11-33 |
| Inventive step (IS) | Yes: | Claims | - |
| | No: | Claims | 1-33 |
| Industrial applicability (IA) | Yes: | Claims | 1-19,28-33 |
| | No: | Claims | - |

2. Citations and explanations

**see separate sheet**

**Box No. VI Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

**see form 210**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

N.1 Claims 20-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, namely methods of treatment of the human/animal body. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. DOCUMENTS and ABBREVIATIONS.

γ-PGA: poly-γ-glutamic acid;
γ-D-PGA: poly-γ-(D)-glutamic acid;
PA: Protective Antigen;
BSA: Bovine Serum Albumin.

Reference is made to the following documents:

D1: Alkan S. S. et Al., *Journal of Immunology* (1971) Vol. 107, No. 2, Pages 353-358;
D2: Goodman J. W. et Al., *Biochemistry* (1968) Vol. 7, No. 2, Pages 706-710;
D3: Klaus G. G. et Al., *European Journal of Immunology* (1975) Vol. 5, No. 2, Pages 105-111;
D4: Senyk G. et Al., *Immunochemistry* (1972) Vol. 9, No. 2, Pages 97-110;
D5: Emmanuel J.-p. & Prodhomme F., *Abstracts of Papers American Chemical Society* (2000) Vol. 219, No. 1-2, Page BIOL133;
D6: Schneerson R. et Al., *PNAS* (2003) Vol. 100, No. 15, Pages 8945-8950;
D7: Leppla S. H. et Al., *Journal of Clinical Investigation* (2002) Vol. 110, No. 2, Pages 141-144;
D8: Welkos S. et Al., *Microbiology* (2001) Vol. 147, No. 6, Pages 1677-1685.

D9: WO 01/60412 A.

1.1 D1 discloses conjugates of γ-D-PGA from B. anthracis and (L)-Tyrosine-azobenzenearsonate eliciting anti-PGA antibodies in guinea pigs challenged with the conjugates (see: abstract; page 354, right-hand column, second paragraph; paragraph joining pages 355 and 356; page 356, paragraph joining left- and right-hand column; page 357, left-hand column, first paragraph).

1.2 D2 discloses rabbit antisera against the γ-PGA capsular polypeptide of B. anthracis prepared by immunization with intact bacilli or the capsular polypeptide complexed with methylated BSA (see: abstract; page 706; right-hand column, lines 10-13).

1.3 D3 discloses immunogenic conjugates of a hapten moiety and γ-D-PGA, which induce an IgM response against the hapten moiety (see the corresponding MEDLINE abstract).

1.4 D4 discloses immunogenic conjugates of glucagon and γ-D-PGA, which elicit cellular and humoral responses to the glucagon moiety (see: abstract; paragraph joining pages 98 and 99).

1.5 D5 and D9 disclose γ-PGA as carrier for drug delivery. In particular, D5 discloses tumour-specific antibodies and anti-cancer agents covalently conjugated to γ-D-PGA moieties from B. licheniformis through thioester linkages (see the abstract). The drug conjugates disclosed in D9 have a disulphide linkage (see claims 1 and 7). In addition, D9 indicates that PGA drug conjugates account for improved drug pharmacodynamic (see the paragraph joining pages 6 and 7).

1.6 D6 discloses conjugates of PA and γ-D-PGA from B. anthracis for the manufacture of vaccines against Anthrax (see in particular: the abstract; page 8946, left-hand column, second paragraph to the end of the first paragraph on page 8947; table 1). As the priority date is considered to be valid, D6 will not be taken into account for the purpose of this Preliminary Examination.

1.7 D7 and D8 disclose Anthrax vaccines comprising PA as the primary immunogenic antigen (see for example the abstract of D8). Both documents indicate that other antigens from the bacilli are involved in the vaccine immunity, for example sera

from immunized individuals cross-reacts with the bacterial spores (see D8: page 1678, left-hand column, lines 7-14; page 1684; right-hand column, lines 24-31). In addition, D7 indicates that antibodies against the bacterial capsule polypeptide γ-D-PGA could also be involved in the immunity to B. anthracis (see page 143, left-hand column, first paragraph). Improved vaccines could therefore contain these additional antigenic specie (see: D7, page 143, right-hand column, first paragraph; D8, paragraph joining pages 1682 and 1683).

2. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT).

2.1 For the assessment of the present claims 20-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.2 Claims 1-19, 32 and 33 relate to immunogenic conjugates of the capsular polypeptide from B. anthracis and compositions thereof. Claims 28-31 relate to antibodies against the capsular polypeptide or its conjugates. Said conjugates, compositions and antibodies can be made in the pharmaceutical industry, hence they are to be considered as having an industrial applicability according to article 33(4) PCT.

3. NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT).

3.1 The subject-matter of claim 1 is not novel over the immunogenic γ-PGA conjugates of D1, D3 and D4 (see points 1.1, 1.3 and 1.4 above). In addition, the subject-matter of claim 1 cannot be considered novel over the γ-PGA-antibody conjugates disclosed in D5 because the immunogenic properties of these conjugates are intrinsic in the antibody component (see point 1.5 above).

3.1[a] Dependent claims 2-5, 7-9, 11-15 and claims 16-27, 32 and 33 do not contain any features which, in combination with the features of any claim to which they refer,

meet the requirements of the PCT in respect of novelty and/or inventive step, given the disclosure of the prior art (see again points 1.1, 1.3-1.5 above). In particular, medical and pharmaceutical applications of the known γ-PGA conjugates are apparent from the prior art.

3.1[b] With respect to claim 5, it is noted that the list of carrier moieties includes mammalian immunoglobulins as disclosed in D5 and known immunogenic adjuvants.

3.2 The subject-matter of claims 6 and 10 is novel over the available prior art in view of the PA moiety conjugated to the γ-PGA polypeptide.

3.2[a] D7 and D8 can be independently considered to represent the relevant state of the art. These documents discloses immunogenic compositions for anthrax vaccines, from which the claimed subject-matter differs in the γ-PGA component covalently conjugated to PA (see point 1.7 above).

3.2[b] The problem to be solved can therefore be regarded as the provision of an improved immunogenic composition for anthrax vaccines.

3.2[c] The prior art explicitly suggests improvements for the anthrax vaccine by incorporating in the PA-based composition additional antigenic epitopes from the bacilli, among which the capsular polypeptide γ-PGA (see again point 1.7 above). In addition, D1 shows the antigenic properties of the γ-PGA epitope in conjugated forms (see point 1.1 above). The skilled person would have combined the teachings of this prior art in order to solve the problem posed, thereby obtaining conjugates according to claims 6 and 10.

3.3 In addition to the lack of conciseness (see below), the subject-matter of claims 28-31 lacks novelty over the anti-γ-PGA antibodies disclosed in D1 and inherently comprised in the sera of D2 (see points 1.1 and 1.2 above).

**Re Item VIII**

**Certain observations on the international application**

4. CLARITY (Art. 6 PCT).

4.1 Although claims 16, 18, 32 and 33 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, and to differ from each other only with regard to the terminology used for the features of that

subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

4.2 A similar observation applies to claims 20 and 24 and claims 28-31, which have been drafted as separate independent claims, despite the fact that they relate to the same subjects, i.e. medical uses of immunogenic γ-PGA conjugates according to claim 1 and antibodies to the γ-PGA polypeptide. Claim 24 and claims 29-31 respectively differ from claims 20 and 28 only in respect to additional features, for which a dependent claim structure is appropriate.